REMARKS

The Amendments

Claim 1 has been amended to specify the components of the immunoconjugate protein by its particular constituents, namely the Fc region of a human IgG1 immunoglobulin and a mutant form of factor VII. These recitations are supported *inter alia* by claim 17 as originally filed. Claim 9 has been amended to maintain its scope as coextensive with claim 1.

Claims 21 and 23 were amended to clarify that the dimers form spontaneously rather than being constructed as such.

New claims 54 recites the presence of a cytotoxic radioactive tag. This is supported at page 12, line 1.

New claims 55-57 each specifies a particular form of mutant factor VII disclosed throughout the specification.

The Specification

The hyperlinks in the disclosure have been removed by this amendment.

Claim Construction

The Patent and Trademark Office construes the claims in certain ways that are not what applicants intended. Applicants therefore clarify the intended meaning of their claims.

The Patent and Trademark Office states that the rejected claims (1, 3, 6-8, and 47) recite a form of factor VII "wherein the mutant form has a serine-344→alanine substitution." In fact, of the rejected claims only claim 3 has this recitation. The other rejected claims, 1, 6-8, and 47[1] were not so limited.

The Patent and Trademark Office states that the term "can" in the claim recitation "can induce a cytolytic immune response or cytotoxic effect" is "open ended." This recitation has been deleted by amendment, rendering this construction moot.

The Patent and Trademark Office further characterizes "the claims" (1-3, 6-8, 46-47) as reciting a mutant factor VII which has lysine-341→alanine and serine-344→alanine substitutions. (Paper No. 20040504, at page 7, lines 3-9). Only claim 46 requires this pair of substitutions.

Rejection of Claims 1, 3, 6-8, and 47 Under 35 U.S.C. § 102(b)

Claims 1, 3, 6-8, and 47[2] are rejected as allegedly anticipated by Nakagaki. This rejection is respectfully traversed.

Claims 1 is the only independent claim of the rejected set of claims. Claims 1 recites: "An immunoconjugate protein comprising an Fc region of a human IgG1 immunoglobulin conjugated to a targeting domain."

[1] Claim 47 is cancelled by this amendment.
[2] Claim 47 is cancelled by this amendment and will not be discussed further.

Nakagaki is cited as teaching a radioiodinated factor VII mutant wherein serine-344 is replaced with an alanine. The radioisotope of Nakagaki is interpreted by the Patent and Trademark Office as fulfilling the claim recitation of an effector domain which induces a cytotoxic effect. Since claim 1 has been amended to replace this claim recitation with "an Fc region of a human IgG1 immunoglobulin" this rejection has become moot.

To reject a claim as anticipated, each and every element as set forth in the claim must be either expressly or inherently described in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q.2d (BNA) 1051, 1053 (Fed. Cir. 1987).

Nakagaki does not anticipate the subject matter of claim 1 because Nakagaki does not teach an immunoconjugate protein comprising "an Fc region of a human IgG1 immunoglobulin." No part of Nakagaki's molecule contains immunoglobulin sequences. Factor VII is a clotting cascade protein, not an immunoglobulin. Radioiodine is also not an immunoglobulin. Thus, Nakagaki's molecule is not an immunoconjugate protein as recited.

For the same reasons, Nakagaki does not anticipate dependent claims 3, 6-8, or new claims 54-57.

Withdrawal of this rejection is therefore proper and requested.

The Rejection of Claim 47 Under 35 U.S.C. § 102(b)

Claim 47 is rejected as anticipated by Contrino. Claim 47 has been cancelled without prejudice to its future prosecution.

The Rejection of Claims 1-3, 6-8, 46-47 Under 35 U.S.C. § 103(a)

Claims 1-3, 6-8, 46-47[3] are rejected as unpatentable over a combination of:

- Olson (*Int. J. Can.* 73:865-870, 1997);
- Drake (*Am. J. Pathobiol.* 134:1087-97, 1989);
- Contrino (*Nature Med.* 2:209-215, 1996);
- Dickinson (*Proc. Natl. Acad. Sci. USA* 93:14379-84, 1996); and
- Berkner (U.S. Patent No. 5,861,374).

Olson is cited for teaching a VEGF-diphtheria toxin conjugate. The conjugate selectively targets tumor vasculature relative to highly vascularized normal tissues.

Drake is cited for teaching that tissue factor (TF) is not expressed on normal vascular endothelial cells but is expressed on cells of several normal tissues and in the adventitial layer of the blood vessel wall. These normal tissues include epidermis, intestinal mucosa, myocardium, bronchial mucosa, alveolar epithelial cells, cerebral cortex, glomeruli, and the capsule and trabeculae of the spleen. Drake is also cited for teaching the binding of factor VII and factor VIIa to TF and its role in the clotting cascade.

Contrino is cited for teaching that TF is expressed on endothelial cells of the tumor vasculature.

[3] Claim 47 has been cancelled.

Dickinson is cited for teaching that amino acid residue lysine-341 of factor VII is important for catalytic function.

Berkner is cited for teaching that the serine-344→alanine substitution in factor VII resulted in decreased blood coagulation activity relative to wild type. Berkner teaches use of the substituted protein as an anti-coagulant.

Claims 1-3, 6-8, and 46 (as amended) are directed to immunoconjugate proteins comprising an Fc region of a human IgG1 immunoglobulin and a targeting domain. The targeting domain is a particular form of factor VII that has a mutation in lysine-341, serine-344, or both, and therefore does not initiate blood coagulation.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art references (or references when combined) must teach or suggest all the claim limitations. M.P.E.P. §2143.

The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in the applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

The rejection urges that it would have been obvious to make an immunoconjugate having factor VII as a targeting domain conjugated to an effector domain such as diphtheria toxin which induces a cytotoxic effect. Because claims 1-3, 6-8, 46-47 have been amended to delete the recitation of a cytotoxic effect and to recite "an Fc region of a human IgG1 immunoglobulin," this rejection should no longer apply to these claims.

1. The cited references do not suggest or teach all the claim limitations.

None of the prior art references teach an immunoconjugate protein. An immunoconjugate protein requires an immunoglobulin or immunoglobulin fragment. See FDA's "Points to consider in the manufacture and testing of monoclonal antibody products for human use, February 28, 1997, at page 13 ("Immunoconjugates are typically produced by chemical processes using specific reagents to link the unconjugated antibody with a non-antibody agent. Alternatively, immunoconjugates can be obtained as chimeric recombinant proteins containing non-immunoglobulin and immunoglobulin sequences in the same polypeptide chain."), attached as Appendix 1. A targeting domain which comprises a Factor VII form is not an immunoglobulin or immunoglobulin fragment. Diphtheria toxin is not an immunoglobulin or immunoglobulin fragment. Thus the immunoconjugate element of claims 1-3, 608, and 46 is missing from the asserted combination of five references.

None of the references teach using "an Fc region of a human IgG1 immunoglobulin." Each of the rejected (and now amended) claims positively recites this element. Thus, this is a second element of the claims which the references do not teach.

The *prima facie* case fails for failing to teach or suggest all elements of the rejected claims.

2. The cited references do not suggest or motivate the claimed combination of references.

Nothing in the cited references suggests or motivates that one should modify the teachings of the primary reference, Olson. Olson teaches a conjugate of VEGF and diphtheria

toxin. Nothing in Olson or the other references suggests modifying both halves of the conjugate: to change VEGF to a form of factor VII and to change diphtheria toxin to an Fc of an IgG1.

The rejection uses the applicant's disclosure as a template to collect various disparate teachings in five different references and carefully to combine the relevant parts and to ignore the irrelevant parts. But this method of making a rejection is improper. See *In re Vaeck, supra.* There simply was no suggestion to combine or modify in the prior art or in the knowledge generally available. For this reason alone, the rejection should be withdrawn.

Because the combination of cited references does not teach all claim elements and because there was no suggestion or teaching to combine or modify the reference teachings, a *prima facie* case has not been made. Withdrawal of this rejection is respectfully requested.

The Rejection of Claims 1-3, 6-8, 21-22, 46-47 Under 35 U.S.C. § 103(a)

Claims 1-3, 6-8, 21-22, and 46-47[4] are rejected over a combination of five references as obvious. The cited references are:

- Thorpe (U.S. Patent No. 6,132,729)
- Min (Cancer Res. 56:2428-33, 1996)
- Contrino (*supra*)
- Dickinson (*supra*)
- Berkner (*supra*)

Claim 1 recites immunoconjugate proteins comprising the Fc region of IgG1 and a factor VII with certain enumerated mutations which are known to block factor VII from initiating the blood coagulation cascade. In particular the mutations are substitutions of alanine for lys-341

[4] Claim 22 and 47 have been cancelled.

and/or ser-344. Each of claims 2, 3, 6-8, 21, and 46 is dependent on claim 1. Claims 2, 3, and 46 specify which mutations in factor VII are present. Claims 6-8 specify a mode of preparing the immunoconjugate. Claim 21 specifies that the immunoconjugate is a homodimer.

Thorpe is cited for teaching:

- Factor VII binds to tissue factor (TF);
- TF is not expressed on blood cells;
- TF is not expressed on normal vasculature;
- TF expression on vasculature causes pathological clotting;
- TF is expressed on many normal tissues and cells;
- Pathological coagulation could lead to metastasis; and
- A toxin can be conjugated to a molecule that targets tumor endothelium.

Min is cited as teaching a fusion protein comprising a domain of mouse urokinase (uPA) and an Fc region of IgG1. uPA is involved in a proteolytic cascade used by tumor cells and endothelial cells for basement membrane invasion. Min's fusion protein inhibits binding of uPA to its receptor. See Fig. 1 and page 2430, column 1. Min teaches that his fusion protein inhibits capillary tube formation by inhibiting uPA binding to its receptor. Min postulates three mechanisms of action of his fusion protein at page 2433, lines 6-15. None of these suggest that anything other than uPA is the active component of the fusion protein. Min does not teach or suggest any other biological function of his fusion protein.

Contrino teaches a biotin-labeled factor VIIa.

Dickinson teaches the importance of factor VII residue lysine-341 for catalytic function. Dickinson teaches that a ser-344→ala mutation is "essentially inactive," having a maximal rate of $< 0.1\ s^{-1}$. See legend to Fig. 1. The lys-341→ala mutation leads to a loss of proteolytic

function of > 3 standard deviations of control. See Fig. 1, Fig. 1 legend, and Table 1 of Dickinson.

Berkner teaches the importance of factor VII residue serine-344 for catalytic function. Berkner teaches that such modified factor VII (ser-344→ala) "exhibited no detectable coagulant activity." Column 14, lines 17-18.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art references (or references when combined) must teach or suggest all the claim limitations. M.P.E.P. §2143. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in the applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

The present rejection fails to present a *prima facie* case because there is no motivation or suggestion in the references themselves to modify the references or to combine the reference teachings, as discussed below.

Min teaches a fusion protein comprising uPA and Fc. The Fc portion of the protein is taught to create a high-affinity uPA receptor antagonist, presumably due to dimerization. Min does not teach or suggest that the Fc portion induces an immune cytolytic response.

Thorpe teaches targeting an immunotoxin to tumor vasculature. "Immunotoxin" is used by Thorpe as an antibody bound to a toxin. See column 7, lines 34-47. Thorpe teaches the use of receptors for VEGF, FGF, and TGF as targets on tumor vasculature. Other targets taught by Thorpe include endoglin, TIE, VCAM-1, P-selectin, E-selectin, α-β integrin, pleiotropin, and

endosialin. Thorpe does not teach or suggest using Factor VII to target TF on tumor endothelium. On the contrary, Thorpe teaches use of TF to target tumor endothelium. None of the references, alone or combined, teaches or suggests a fusion of Factor VII with an Fc of an IgG1.

The rejection urges that one of skill in the art would have sought "to inhibit initiation of the coagulation pathway because Thorpe et al. teach that tissue factor is expressed in normal tissue and binding of an administered active factor VII-Fc immunoconjugate could induce disseminated intravascular coagulation." Paper 20040504, page 15, lines 7-10. Yet, this reasoning is diametrically opposed to what Thorpe actually states:

> The essence of the invention may also be defined as a composition comprising at least a biologically effective amount of at least a first coagulation-deficient Tissue Factor compound for use in the preparation of a medicament for use in promoting coagulation preferentially, or specifically, in prothrombotic blood vessels of an animal, particularly those associated with a benign or malignant disease site.

Column 3, lines 53-59, emphasis added.

Moreover, Thorpe actually proposes administration of native Factor VIIa sufficient to increase coagulation:

> In certain embodiments, the Tissue Factor compound will be a mutant Tissue Factor deficient in the ability to activate Factor VII. Although useful alone, the most preferred uses of such mutants will be in conjunction with the co-administration of a biologically effective amount of at least one of Factor VIIa or an activator of Factor VII, such as when used with an amount of Factor VIIa sufficient to increase tumor vasculature coagulation and tumor necrosis in the animal.

Column 5, lines 57-65, emphasis added. This directly contradicts the motivation posited by the rejection. Thus, Thorpe does not teach or motivate one of skill in the art to modify either his own constructs or Min's constructs to make the constructs of the present

invention as asserted in the rejection. Thorpe aims to ***promote coagulation*** while the present invention employs mutants which do not initiate blood coagulation. As cited above, Dickinson and Berkner teach that the recited factor VII mutations lead to forms of factor VII that are ***inactive*** for initiation of blood coagulation.

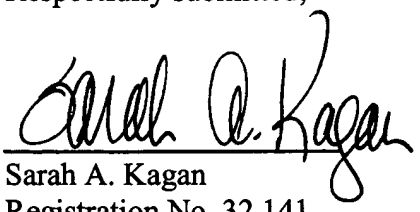
None of Dickinson, Contrino, or Berkner provides motivation or suggestion to modify or combine the teachings of Min, Thorpe, Dickinson and/or Berkner. Contrino is cited for teaching a biotin-labeled factor VIIa. Dickinson and Berkner are cited for teaching the importance of residues 341 and 344 for catalytic function of factor VII. None of these would motivate or suggest that the elements of the claimed invention ought to be combined.

The prior art does not teach or suggest making the modifications or combinations required to achieve the present invention. Thorpe actually teaches away from making the present invention by teaching the desirability of increasing coagulation in a tumor patient and teaching administration of native factor VII. The motivation to make the present invention asserted by the Patent and Trademark Office appears to come straight from applicants' own specification. Such hindsight reconstruction using an applicant's own teaching has been thoroughly discredited as a basis for making a *prima facie* case of obviousness. See *In re Vaeck, supra.*

Because the prior art does not teach or suggest the claimed invention, the rejection should be withdrawn and the claims passed to issuance.

Respectfully submitted,

Dated: August 16, 2004

By: 

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